Approach to Renal Failure

Introduction

Acute kidney injury is a rather vague term. Clinically, we use AKI to refer to an elevated creatinine, a sign of reduced GFR, which is also a sign of the cells of the kidney suffering some metabolic derangement. "*If the creatinine is elevated, something is wrong with the kidney.*" Good enough for clinicals, but as we discuss acute kidney injury from a mechanism's perspective, from a basic sciences lens, we have to be more specific. Everything in this introduction section is review. It compiles all the lessons of the kidney series, orienting you from what you know already to how we approach kidney injury.

You should consider every nephron to be two different systems that, while related, should be thought of as independent—the glomerulus and the tubules. The **glomerulus filters** while the **tubules reabsorb**. There is one blood supply to every nephron, yet there are two functions of blood in every nephron. This fact is supported by the fact that there are two capillary beds in series—one in the glomerulus and one around the cells of the tubules.

The capillary bed in the glomerulus influences **glomerular filtration rate** (GFR)—how much filtrate is generated into the tubules. Flow into and through the glomerulus provides alterations in hydrostatic forces that regulate GFR (Kidney #3: *Glomerular Filtration*). In order to generate a filtration force, there has to be enough blood flow into the glomerular capillary (perfusion pressure) and a favorable balance of hydrostatic forces to push filtrate through into Bowman's capsule. Constriction of the efferent arteriole increases the hydrostatic force within the capillary; dilation of the efferent arteriole decreases it. Constriction of the afferent arteriole decreases the hydrostatic force within the capillary; dilation increases it. In physiology, we essentially ignored hydrostatic forces pushing back on capillaries from Bowman's space, because that force was negligible. Now in considering pathology, the back pressure must also be considered. Obstruction to renal drainage translates back pressure to every nephron, increasing the hydrostatic forces from Bowman's capsule back into the glomerulus. At the level of the glomerular capillary, oncotic forces do not play a role in filtration.

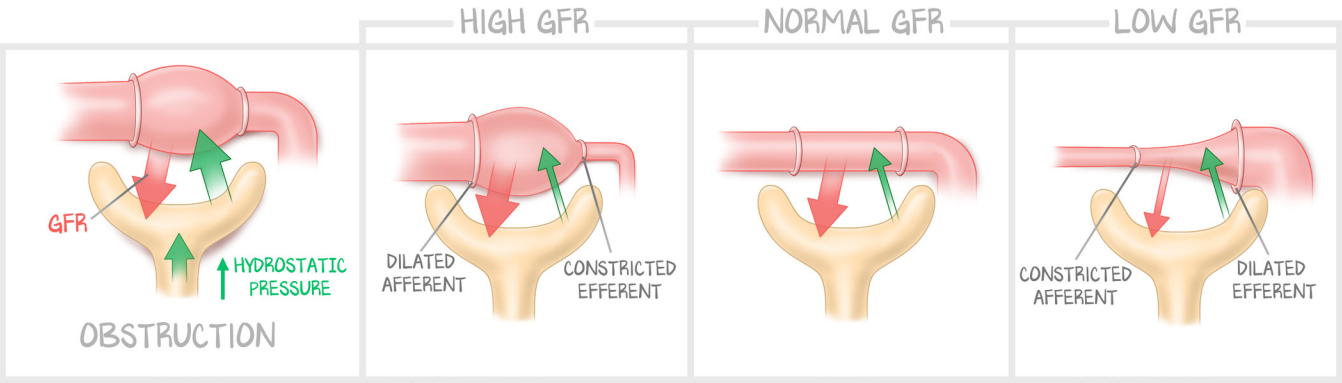


Figure 1.1: Arterioles' Impact on GFR
This image serves as a reminder that at the glomerulus, only hydrostatic forces change the glomerular filtration rate. The afferent arteriole controls inflow—dilation increases GFR; constriction reduces GFR. The efferent arteriole controls outflow—constriction increases GFR; dilation decreases GFR. In addition, since hydrostatic forces alone matter at the glomerulus, under pathologic conditions, in addition to afferent and efferent arteriole mechanics, increases in hydrostatic pressure from Bowman's space must now be accounted for. Oncotic forces do not affect GFR.

The blood urea nitrogen (BUN) and the creatinine (Cr) are both filtered by the glomerulus. We use creatinine as a surrogate for GFR. Both the BUN and creatinine will rise because of a failure to filter, because of a reduced GFR, because of a problem with filtration forces. Notice it is filtration forces that

affect creatinine levels. Either capillary hydrostatic pressure could fall or elevated hydrostatic pressure from Bowman's space could rise. You will see this manifested as prerenal (capillary hydrostatic pressure falling) and postrenal (Bowman's space hydrostatic pressure increasing).

The capillary bed around the tubules serves the usual purpose of every other capillary bed not alveolar or glomerular—**oxygen delivery**. The epithelium of the tubules is intensely metabolic. Reabsorption of filtrate is dependent on establishing a favorable sodium gradient to move solutes into the cells from the lumen. That favorable sodium gradient is established by the **Na^+/K^+-ATPase**, with an emphasis on ATP. The countercurrent exchange and the concentration gradient from cortex to medulla, essential for the reabsorption of filtered water the PCT couldn't reabsorb, is dependent on actively pumping salt (sodium) out of the cell. That is achieved with the **Na^+/K^+**-ATPase.

Everyone teaches that the renal plasma flow influences the glomerular filtration rate. It does. "*More in, less out*" would increase the hydrostatic forces of the glomerular capillary favoring filtration. "*More in*" means an increase in blood flow into the glomerular capillary. But we have adjusted your perspective to see that the glomerular filtration rate has to do with the relative constriction of the afferent and efferent arterioles. "*More in*" in the OME orientation means "dilated afferent arteriole." "*Less out*" means constricted efferent arteriole. We want you to see that **renal blood flow** is the amount of blood that gets past both afferent and efferent arterioles and affects the capillaries of oxygen delivery only.

Creatinine is not reabsorbed by the tubules. BUN is reabsorbed by the tubules. If filtration is impaired but the tubules still work, what little BUN is filtered is easily reabsorbed. The BUN and creatinine rise, but the BUN being reabsorbed increases much more. If reabsorption is impaired because of tubule damage, because of a failure of the tubules, BUN will not be reabsorbed. And while BUN and Cr do rise, because BUN will not be reabsorbed, they rise in parallel to one another. This is a manifestation of intrarenal kidney disease.

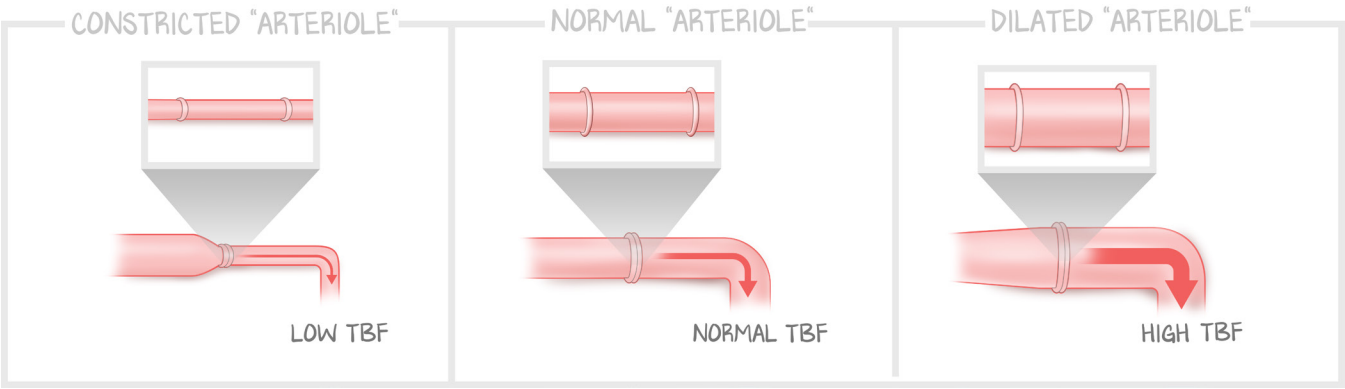


Figure 1.2: Arterioles' Impact on RBF
The flow of blood delivered to the peritubular capillaries is the result of the summed forces of the afferent and efferent arterioles, represented here as a single combined arteriole. When the "combined arteriole" is constricted, less flow gets to the peritubular capillaries. When the "combined arteriole" is dilated, more flow gets to the glomerular capillaries.

Filtration is based on the relative constriction of arterioles, the pressure *between* the two arterioles. Renal blood flow is based on the pressure *after* both arterioles. The blood into the nephron, the state of relative vasoconstriction or vasodilation of each arteriole, and the blood flow into the peritubular capillaries ARE interrelated. We insist that you intentionally separate them.

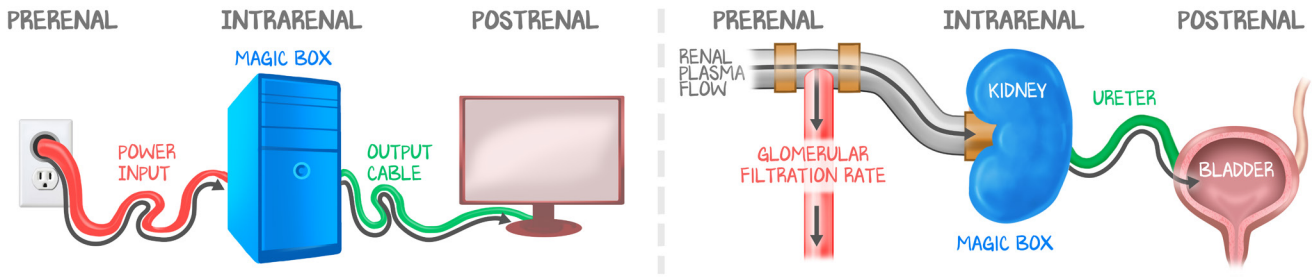
We're going to explore the approach to kidney injury. First, with an analogy most people inherently understand. Then we'll do it again with the kidney. Finally, we cover the tubulointerstitial diseases.

Approach to Kidney Injury

Think about the last desktop computer you bought. It had a tower, a monitor, and some accessories. The computer tower is where the motherboard, the video card, and all that magical black box stuff happens. The computer monitor is the output, it's what the computer is showing you. In order to get the output you want, there were a few things you had to do.

If you just set the computer monitor on the desk, then tower next to it, not much would happen. The screen is black. What's the first thing you check? **Is the power plugged in**—is there supply to the magic box? So, you plug in the power cables and turn the computer on. The computer whirs, links blink, but the monitor is still dark. What's next? **Is the monitor cable attached—**is there a connection between the magic box and the computer monitor. At that point, most monitors just work. You solved it by taking care of the pre-magic box (the power) and the post-magic box (the monitor cable). Think how many times, when your monitor didn't come on, that you opened up the tower and fiddled with the parts inside. Most people have never done that. Going **into the magic box** is generally not a good idea.

Notice what we did. The inherent flow of electrons is 1. Power—2. Computer—3. Monitor cable. But we assessed the computer's function 1. Power—2. Monitor cable—3. Computer. We did pre, post, intra, in that order. **So too will your approach to renal failure be PRE, POST, then INTRA**. The kidney is the magic box. The "pre," the power to a kidney, is the perfusion to the kidneys and what the arterioles are doing (GFR and RBF). The "post" of the kidneys is what the kidneys make, urine. The "monitor cable" is the ureters and bladder. The "intra," the magic box, is the kidney. This long drawn-out analogy to the computer is to reinforce that most causes of kidney disease are diagnosed not with a kidney biopsy (going into the magic box), but by using the history, physical, and laboratories. You will learn much about kidney biopsies in Basic Sciences. Know that, most of the time, the diagnosis is made without one.



(a) (b)

Figure 1.3: Approach to Renal Failure
(a) Monitor example labeled. (b) Kidney model labeled.

Prerenal Injury

Prerenal means **not enough perfusion to the kidneys**. But be careful here. There is not enough perfusion to the kidneys to provide the necessary hydrostatic forces to favor filtration. There is still enough perfusion of the kidney to satisfy the oxygen demands of the tubules. In prerenal azotemia there is no loss of the tubule epithelium, no hypoxia of the nephrons, only a failure to filter the blood. Since there is less filtration, there is less water, ions, and other solutes to reabsorb. Initially, with less filtered, there is less absorbed, and a lower metabolic demand on the epithelial cells.

In this case, neither BUN nor creatinine are filtered as well as they should be. What BUN is filtered is easily reabsorbed. The BUN and Cr rise. The BUN rises more because it is reabsorbed. A **BUN:Cr ratio greater than 20** is indicative of prerenal injury.

In this case, less sodium is filtered. Sodium is easily reabsorbed. Since less is filtered and the same amount is reabsorbed, the fractional excretion of sodium will be low. A **FENa < 1%** is indicative of prerenal injury.

In this case, less water is filtered. Water is easily reabsorbed. Since less water is filtered and the same amount is reabsorbed, there will be a **low volume** of **concentrated urine** (> 300 Osms).

Let's do that again using the Katrina switch. Blood flow to the glomerulus is low. Perfusion pressure is low, so filtration forces are low. Less fluid filtered means less flow through the nephron. The macula densa senses a low flow, the switch falling by gravity to on. The macula densa tells the JG cells to release renin. Increased renin means increased angiotensin 2. Increased angiotensin 2 means increased aldosterone. Increased aldosterone means an increase in ENaC channels in the collecting duct. More sodium is reabsorbed, reducing the fractional excretion of sodium. The posterior pituitary responds to a similar stimulus—increased angiotensin 2 and low blood volume results in ADH release. ADH inserts aquaporin channels in the collecting duct. More water is reabsorbed.

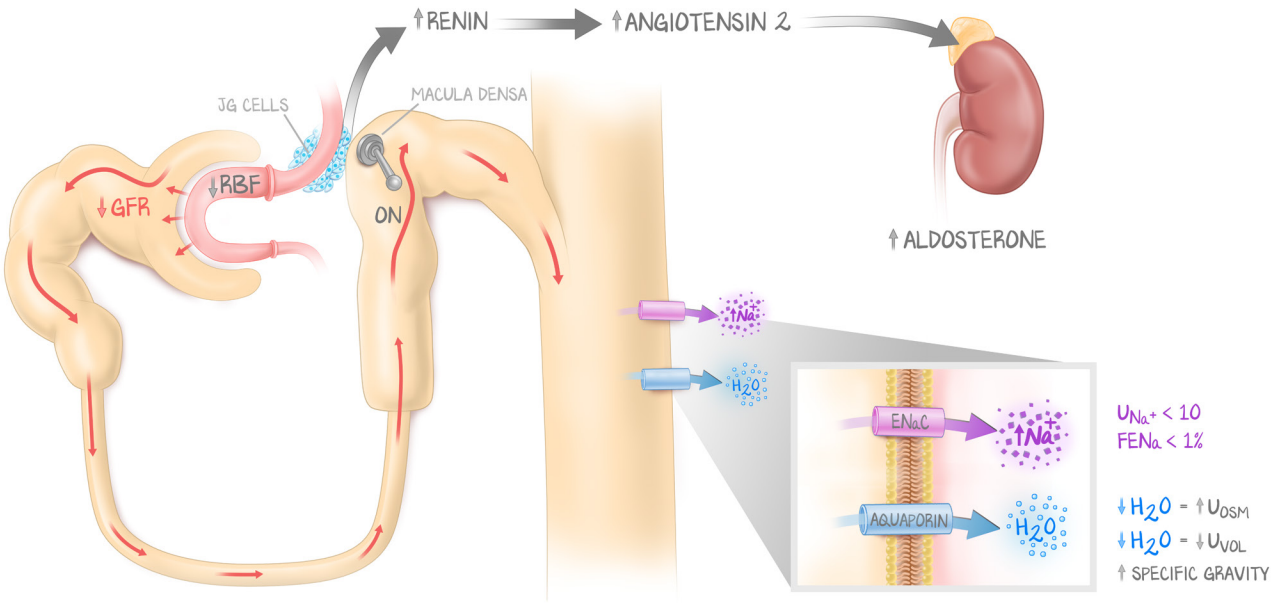


Figure 1.4: Prerenal Katrina Switch
Since GFR is reduced, flow through the nephron is reduced. The switch falls, by gravity, to ON. Renin goes up, Ang-2 goes up, and therefore aldosterone and ADH go up. Aldosterone reabsorbs sodium via ENaC channels; ADH reabsorbs water via aquaporins. The urine volume goes down and concentration goes up.

Remember that the reabsorption of the PCT, the concentrating of the descending loop of Henle, and the diluting of the ascending loop and DCT are not impacted by prerenal azotemia because they are still getting sufficient oxygen. The variation in fractional excretion and urinary concentration is regulated by the collecting duct. In a prerenal state, activation of the RAAS causes sodium and water to be reabsorbed.

But what else does activation of the RAAS do? Angiotensin 2 vasoconstricts the afferent and efferent arterioles. Because of the myogenic response, the vasoconstriction effect is felt more on the efferent arteriole. This is an attempt to **correct filtration pressure** by increasing the resistance in the efferent

arteriole, generating more hydrostatic force in the capillary. The macula densa senses low filtration flow and attempts to correct filtration flow. But the byproduct of constricting both arterioles is an increased overall resistance, and therefore reduced blood flow, reduced oxygen delivery to the tubules. **Prerenal azotemia**, if prolonged, **results in ischemia of the tubules**. We'll come back to that when we discuss intrarenal disease, later this lesson.

Postrenal = Obstruction

Postrenal means distal to the collecting duct—pelvis, ureters, bladder, and urethra. Postrenal causes of renal failure are all **obstructions**. The kidneys sustain a fairly constant rate of urine formation. Urine is supposed to drain into the bladder. The bladder can vary in size until the person chooses to empty it. The release of urine happens very quickly through the urethra. But all the while, whether the person is holding the urine in or releasing it from the bladder, the kidneys continue to make urine at about the same rate as always.

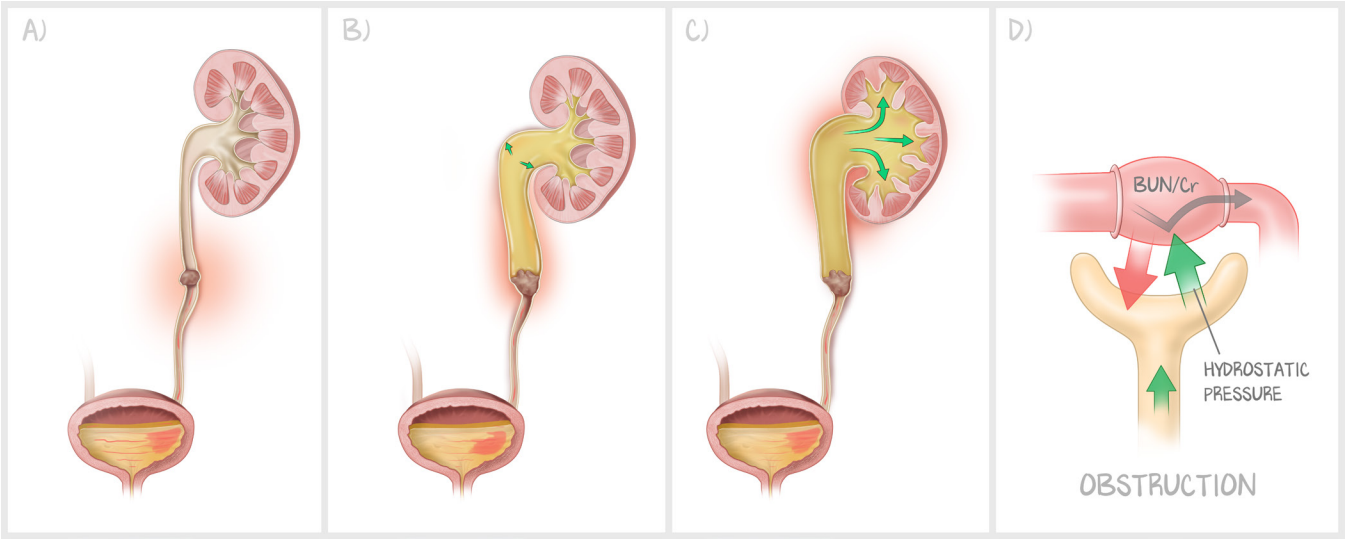


Figure 1.5: Postrenal Obstruction Effects
A stone blocks the flow of urine. As more urine is made, the ureters distend first to accommodate the extra volume. Then as they stretch too far, the calyces dilate to accommodate the volume. Eventually, they stretch too far as well, and the forces pushing back on the overstretched calyces is translated to the tubules, ultimately increasing the hydrostatic forces from Bowman's space, preventing the filtration of BUN and Cr.

If there is an obstruction of that flow, the kidneys don't stop making urine. It's easiest to consider this from the perspective of the ureter. The ureter is a tube. That tube is now blocked. Distal to the obstruction, urine still flows without difficulty, and the ureter is normal. Proximal to the obstruction, more and more urine is produced, accumulating. The ureters and pelvis are transitional epithelium, which means they can distend to accommodate excess urine. That dilation is called **hydroureter**. When that dilation occurs in the pelvis and collecting system, it is called **hydronephrosis**. "*Hydro*" is the sign of obstruction.

As more volume is added to a closed system, the pressure increases. The hydrostatic force within the collecting system is translated to the nephron, specifically to the glomerulus. The **hydrostatic force of the Bowman's space opposes the hydrostatic force from the capillary**. GFR falls. Less BUN and creatinine are filtered. Their levels rise in the blood. In obstructive uropathy, there is no change in renal blood flow, so the tubules are well perfused.

The obstruction can be at the level of the kidneys (the pelvis), ureter, bladder, or urethra. The list is not long—stones, cancer, neurogenic bladder, and BPH. If you suspect an obstruction, you can eliminate the bladder as the cause by inserting a **catheter**. If the obstruction was at the level of the urethra or bladder, the bladder would have lots of urine in it, and passing the catheter, a massive void would follow. But if the obstruction is at the level of the ureters or higher, then the only way to check is to look with imaging, **renal ultrasound** being preferred, but a **CT scan of abdomen** can also detect hydro. Release of the pressure is the only way to undo the damage. That might come in the form of nephrostomy tube (proximal release), stenting (intra-ureter release), or simply facilitating passage of the obstruction (catheter in the bladder).

Labs are not useful to determine obstructive uropathy—only imaging will help.

Intrarenal Glomerular Disease

Intrarenal is the black box. Rarely do you go into the kidney to find out what is wrong (kidney biopsies are not common for most causes of kidney injury). Intrarenal is further subdivided into glomerular, tubular, and interstitial disease.

Glomerular diseases are the hard ones. We have three lessons dedicated to glomerular diseases. The glomerular diseases are either **nephritic** (**red blood cell casts**, hyperproliferation, diseases of the mesangium and endothelium), or they are **nephrotic** (proteinuria, diseases of the filtration slit). The next lesson (Injury #2: *Tubulointerstitial Diseases*) sets up the mechanics and the advanced organizer for studying glomerular diseases. The two that follow (Injury #3: *Glomerular Filtration* and Injury #4: *Nephrotic Syndrome*) cover the highest-yield glomerular diseases.

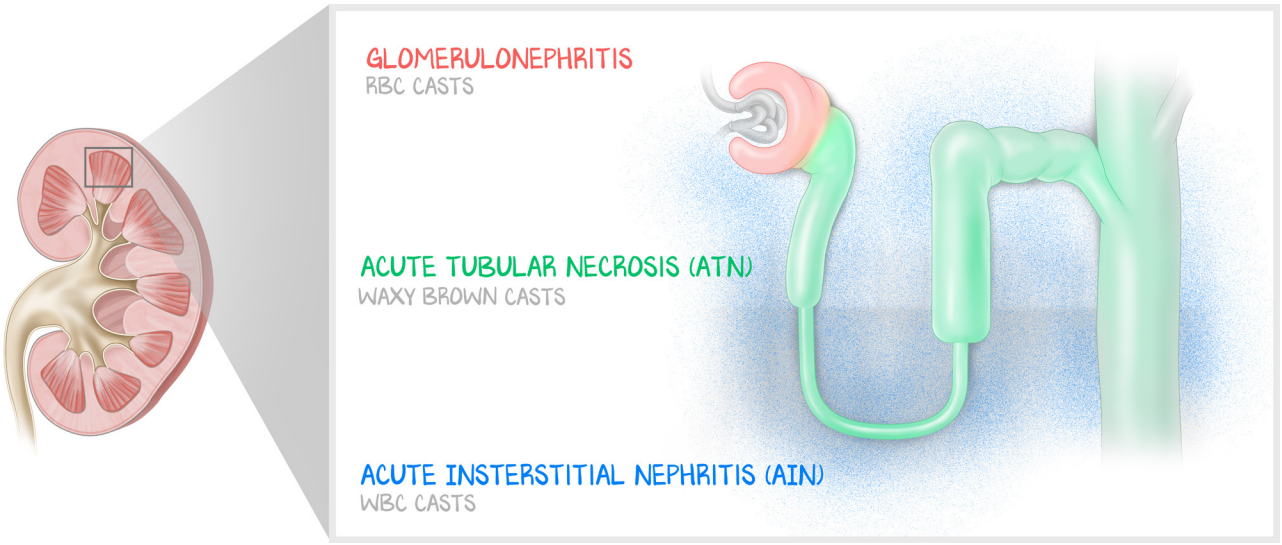


Figure 1.6: Intrarenal Kidney Disease
A schematic showing the distinction between tubular diseases, interstitial diseases, and glomerular diseases, as well as their associated cast findings.

In clinical practice, you will see far more tubulointerstitial diseases (Injury #2: *Tubulointerstitial Diseases*) than you will glomerular diseases. On your licensing exams, you are more likely to see glomerular disease be tested because they focus on fundamental mechanisms more than presentation. Diseases of the tubule cells themselves are referred to as **acute tubular necrosis**. Dying cells will form **waxy brown casts**. Diseases of the interstitium are caused by infiltration by leukocytes, and are termed **acute interstitial nephritis**. Leukocytes form **WBC casts** and there may be **urine eosinophilia**.

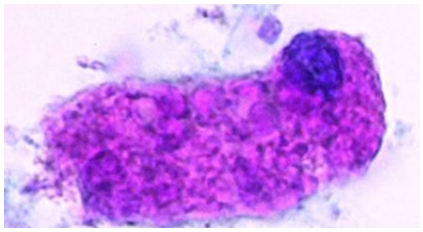
Casts

Look at the urine. If there is a disease of the nephron (glomerulus, tubules, or in between), there will be **casts**. Casts are an amalgam of cells. When they end up in the tubules they mash together and form the shape of the tubules. Some of these casts stay intact as they reach the urine.

Red blood cell casts mark nephritic disease, disease of the glomerulus.

White blood cell casts mark interstitial nephritis. When present with bacteria, that is pyelonephritis.

Muddy brown casts mark acute tubular necrosis.



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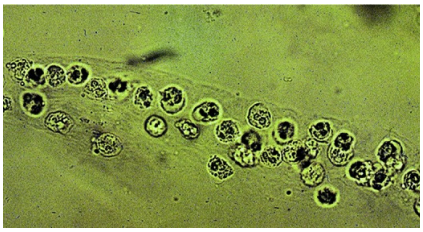

(b)

(c)

Figure 1.7: Urinary Casts
(a) RBC casts. (b) WBC casts. (c) Muddy brown casts.

Reviewing the Approach to Kidney Injury

The creatinine is elevated. We need to deduce why.

We assess prerenal injury first. Is there a sufficient filtration pressure? Laboratories give us the hint—a BUN:Cr > 20 and a FENa < 1% suggest prerenal disease. The question becomes why are they prerenal? Do they have a history that would make them volume-down, such as lack of access to volume or increased insensible water loss like sepsis? Do they have the physical exam which would suggest volume overload, indicative of third spacing fluid? If so, the labs and the history are congruent, and they are prerenal.

We assess postrenal injury second. This assessment actually occurs concurrently, but mentally, do it in this order. Do they have urinary output, pain, or evidence of distention—at the bladder, ureter, or kidney? This is demonstrated with ultrasound. If there is an obstruction, alleviate the obstruction.

We assess intrarenal third. Look at the urine. Are there casts? White blood cell casts suggest interstitial nephritis, waxy brown casts suggest acute tubular necrosis, red blood cell casts suggest glomerulonephritis, and frank proteinuria suggests nephrotic syndrome. Look for triggers (which you will learn in the subsequent lessons) to confirm.

Did you see a biopsy in that discussion? No. Go into the magic box as the last step, and even then, very rarely. Prepare yourself for the next few lessons, where biopsy results are discussed.

Clinical Perspective

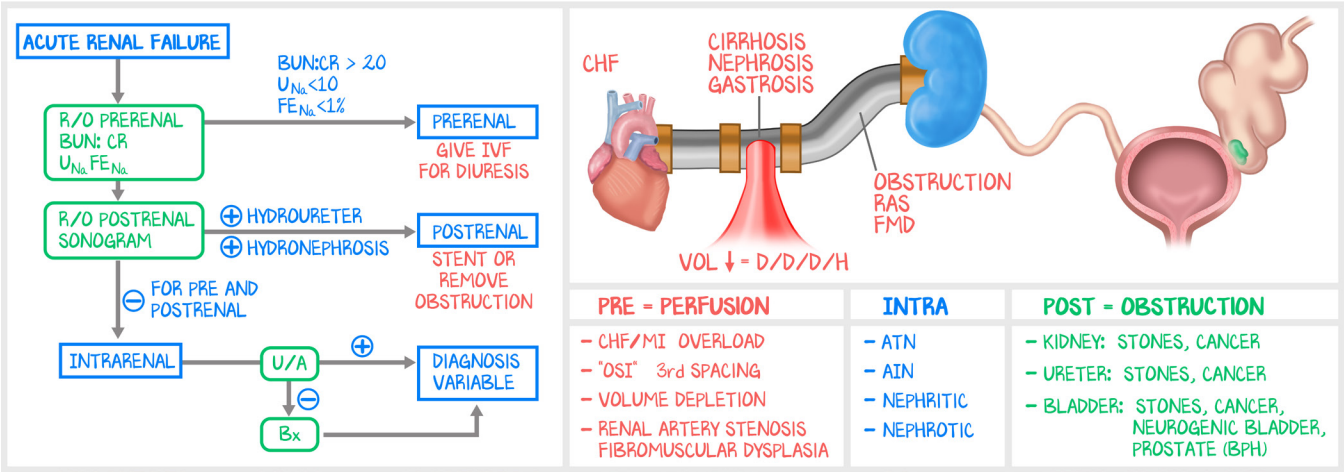

Figure 1.8: Clinical Perspective on Renal Injury
A preview of how you will use this information in clinical medicine, the steps to take to deduce the cause of renal injury, and how having an approach to a problem, rather than memorizing facts, can aid in actual practice.